original article

doi:10.1093/annonc/mdr025
Published online 17 March 2011

Metabolic syndrome and the risk of breast cancer in postmenopausal women

V. Rosato[1], C. Bosetti[1]*, R. Talamini[2], F. Levi[3], M. Montella[4], A. Giacosa[5], E. Negri[1] & C. La Vecchia[1,6,7]

[1]Department of Epidemiology, Istituto di Ricerche Farmacologiche Mario Negri, Milan; [2]Unit of Epidemiology and Biostatistics, Centro di Riferimento Oncologico, IRCCS, Aviano, Italy; [3]Cancer Epidemiology Unit and Cancer Registry of Vaud, Institute of Social and Preventive Medicine, University of Lausanne, Lausanne, Switzerland; [4]Department of Epidemiology, Istituto Nazionale Tumori ''Fondazione Pascale'', Naples; [5]Department of Gastroenterology and Nutrient Unit, Policlinico di Monza, Monza; [6]Department of Occupational Medicine, Università degli Studi di Milano, Milan, Italy; [7]International Prevention Research Institute, Lyon, France

Received 24 November 2010; revised 12 January 2011; accepted 17 January 2011

Background: Only a few small studies investigated the association between postmenopausal breast cancer and metabolic syndrome (MetS) as a single entity.

Materials and methods: We analyzed the data of two Italian and Swiss case–control studies conducted between 1983 and 2007, including 3869 postmenopausal women with incident breast cancer and 4082 postmenopausal controls admitted to the same hospitals as cases for acute conditions. MetS was defined as the presence of at least three components among diabetes, drug-treated hypertension, drug-treated hyperlipidemia, and obesity.

Results: The odds ratios (ORs) of postmenopausal breast cancer were 1.33 [95% confidence interval (CI) 1.09–1.62] for diabetes, 1.19 (95% CI 1.07–1.33) for hypertension, 1.08 (95% CI 0.95–1.22) for hyperlipidemia, 1.26 (95% CI 1.11–1.44) for body mass index ≥30 kg/m^2, and 1.22 (95% CI 1.09–1.36) for waist circumference ≥88 cm. The risk of postmenopausal breast cancer was significantly increased for women with MetS (OR = 1.75, 95% CI 1.37–2.22, for three or more MetS components, *P* for trend for increasing number of components < 0.0001) and the risk was higher at older age (OR = 3.04, 95% CI 1.75–5.29, at age ≥70 years for three or more MetS components).

Conclusions: This study supports a direct association between MetS and postmenopausal breast cancer risk.

Key words: breast cancer, diabetes, hyperlipidemia, hypertension, metabolic syndrome, obesity

introduction

The metabolic syndrome (MetS) is defined as a cluster of metabolic disturbances, i.e. abdominal obesity, insulin resistance, dyslipidemia, and hypertension [1]. MetS was first described in 1988 and identified as a risk factor for cardiovascular diseases, and only more recently, it was associated to the risk of various common cancers [2, 3], including hormone-related cancers [4].

Several studies reported a direct association between individual components of MetS and breast cancer risk in postmenopausal women, in particular overweight and diabetes [5, 6]. However, only a few small studies investigated MetS as a single entity. An Italian nested case–control study on 163 postmenopausal women with breast cancer found that MetS (defined as the presence of three or more components) was significantly associated with breast cancer risk [relative risk (RR) of 2.48 for three or more components compared with none], with a significant trend in risk for increasing number of components [7]. A cohort study of the Metabolic Syndrome and Cancer (Me-Can) Project found no increased risk of breast cancer in relation to MetS (defined as a continuous score) in 2094 women older than 60 years, but an increased breast cancer mortality in 339 women older than 60 years (RR, 1.23 for 1-unit increment of score) [8]. In a US cohort study on 4888 women with baseline and serial measurements of waist circumference, fasting glucose, high-density lipoprotein (HDL) cholesterol, triglycerides, and systolic and diastolic blood pressure, MetS at baseline was not associated with breast cancer risk in 165 postmenopausal breast cancer cases, although in time-dependent covariates analyses, it was directly associated to some increase in risk [9]. An Italian case–control study on 210 postmenopausal breast cancer cases reported that MetS (defined as the presence of at least three components) was more frequent in case than in control women, with an odds ratio (OR) of 1.31 for one or two MetS components and of 1.69 for three or more components compared with none [10].

To provide further information on the association between components of MetS (both individually and combined) and the risk of breast cancer in postmenopausal women, we pooled the data of two case–control studies conducted in Italy and Switzerland [11–13].

*Correspondence to: Dr C. Bosetti, Department of Epidemiology, Istituto di Ricerche Farmacologiche Mario Negri, Via Giuseppe La Masa 19, 20156 Milan, Italy. Tel: +39-023-901-4526; Fax: +39-023-320-0231; E-mail: cristina.bosetti@marionegri.it

materials and methods

We analyzed data from two hospital-based case–control studies: the first one was conducted between 1983 and 1994 in the greater Milan area and included 1988 postmenopausal women with breast cancer (median age 61 years, range 33–86 years) and 1870 postmenopausal controls (median age 60 years, range 37–80 years) [11]; the second one was conducted between 1991 and 2007 in six Italian areas and in the Swiss Canton of Vaud and included 1881 postmenopausal women with breast cancer (median age 61 years, range 33–78 years) and 2212 postmenopausal controls (median age 62 years, range 34–79 years) [12, 13]. Overall, the present analysis included 3869 postmenopausal cases, with incident histologically confirmed breast cancer, admitted to major teaching and general hospitals of the study areas, and 4082 postmenopausal controls, selected among women admitted to the same hospitals as cases for a wide spectrum of acute nonneoplastic diseases, not related to hormonal or gynecological conditions. Controls were comparable to cases in terms of age and study center. Seventeen percent of them were admitted for traumas, 27% for nontraumatic orthopedic disorders, 21% for acute surgical conditions, 10% for eye diseases, 10% for skin disorders, and 15% for various other illnesses (such as dental, ear, nose, or throat disorders). On average, <5% of subjects approached for interview refused to participate.

All subjects were interviewed by *ad hoc* trained interviewers during their hospital stay, using similar structured questionnaires, including information on sociodemographic factors, anthropometric variables, lifestyle habits (e.g. alcohol drinking and dietary habits), personal history of selected medical conditions, menstrual and reproductive factors, and use of exogenous hormones, including hormone replacement therapy (HRT).

Body mass index (BMI) was computed according to Quetelet's index (weight/height^2, kg/m^2). Waist circumference (2 cm above the umbilicus) was measured by interviewers on 3682 (1747 cases and 1935 controls) women from the second study only. History of medical conditions including diabetes, drug-treated hypertension, drug-treated hyperlipidemia, and clinical obesity was self-reported and included age at first diagnosis. Diseases whose onset was <1 year before hospital admission, were not considered.

MetS was defined as the combined presence of: (i) diabetes; (ii) drug-treated hypertension; (iii) drug-treated hyperlipidemia (as a proxy indicator of elevated triglycerides and reduced HDL cholesterol levels); and (iv) abdominal obesity, defined as a waist circumference ≥88 cm or BMI ≥30 kg/m^2, when the information for waist circumference was missing.

statistical analysis

We estimated the OR and the corresponding 95% confidence intervals (CIs) for MetS by unconditional multiple logistic regression models [14], including terms for age (quinquennia), study center, study period, education (<7, 7–11, ≥12 years), alcohol consumption (0, 1, 2, ≥3 drinks/day), age at menarche (<12, 12, 13, ≥14 years), parity and age at first birth (nulliparous, <20, 20–23, 24–27, 28–31, ≥32 years), age at menopause (<45, 45–49, 50–52, ≥53 years), HRT use (never, ever), and family history of breast cancer (no, yes). All statistical analyses were carried out with SAS 9.1 statistical software (SAS Institute, Cary, NC).

results

Table 1 presents the distribution of postmenopausal breast cancer cases and controls according to age, education, and other selected covariates. Cases and controls were comparable in terms of age; as compared with controls, cases reported a higher level of education, more frequent alcohol consumption, earlier age at menarche, later age at first birth and at menopause, a more frequent HRT use and family history of breast cancer.

Table 1. Distribution of 3869 postmenopausal women with breast cancer and 4082 postmenopausal controls according to age, education, and other selected variables (Italy and Switzerland, 1983–2007)

Characteristic	Cases		Controls	
	No.	%	No.	%
Age (years)				
<50	188	4.9	276	6.8
50–59	1470	38.0	1475	36.1
60–69	1708	44.1	1718	42.1
≥70	503	13.0	613	15.0
Education (years)[a]				
<7	2174	56.4	2491	61.3
7–11	1048	27.2	1036	25.5
≥12	633	16.4	537	13.2
Alcohol consumption (drinks/day)[a]				
<1	1761	45.5	2120	52.0
1	826	21.4	818	20.0
2	881	22.8	854	20.9
≥3	401	10.3	289	7.1
Age at menarche (years)[a]				
<12	631	16.3	635	15.6
12	786	20.4	796	19.5
13	905	23.4	879	21.5
≥14	1539	39.9	1769	43.4
Age at first birth (years)[a]				
Nulliparous	723	18.7	705	17.3
<20	153	4.0	263	6.4
20–23	818	21.1	1087	26.7
24–27	1090	28.2	1136	27.9
28–31	679	17.5	558	13.7
≥32	405	10.5	327	8.0
Age at menopause (years)[a]				
<45	645	16.7	873	21.4
45–49	1058	27.4	1150	28.2
50–52	1326	34.4	1305	32.0
≥53	828	21.5	747	18.4
Hormone replacement therapy				
Never	3397	87.8	3692	90.5
Ever	472	12.2	390	9.5
Family history of breast cancer				
No	3402	87.9	3887	95.2
Yes	467	12.1	195	4.8

[a]The sum does not add up to the total because of some missing values.

Table 2 shows the distribution of cases and controls according to individual components of MetS, and the corresponding OR, by study and in the combined dataset. In the two studies combined, the OR of postmenopausal breast cancer was 1.33 (95% CI 1.09–1.62) for diabetes, 1.19 (95% CI 1.07–1.33) for hypertension, 1.08 (95% CI 0.95–1.22) for hyperlipidemia, 1.26 (95% CI 1.11–1.44) for BMI ≥30 kg/m^2, and 1.22 (95% CI 1.09–1.36) for waist circumference ≥88 cm or BMI ≥30 kg/m^2 when information on waist circumference was missing. The estimates were consistent in the two studies, except for diabetes: (OR = 1.00, 95% CI 0.75–1.33 in the first study and 1.72, 95% CI 1.30–2.27 in the second one). None of the OR materially changed by simultaneous adjustment for the other components.

Table 2. Distribution of 3869 postmenopausal women with breast cancer and 4082 postmenopausal controls, and corresponding odds ratios (ORs) with 95% confidence intervals (CIs), according to the individual components of the metabolic syndrome (Italy and Switzerland, 1983–2007)

Component	First study (1983–1994)		Second study (1991–2007)		All
	Cases : controls	OR (95% CI)[a]	Cases : controls	OR (95% CI)[a]	OR (95% CI)[a]
Diabetes					
No	1878 : 1762	1[b]	1753 : 2105	1[b]	1[b]
Yes	110 : 108	1.00 (0.75–1.33)	128 : 107	1.72 (1.30–2.27)	1.33 (1.09–1.62)
Hypertension					
No	1464 : 1457	1[b]	1342 : 1617	1[b]	1[b]
Yes	524 : 413	1.27 (1.09–1.48)	539 : 595	1.14 (0.99–1.32)	1.19 (1.07–1.33)
Hyperlipidemia					
No	1763 : 1687	1[b]	1485 : 1793	1[b]	1[b]
Yes	225 : 183	1.10 (0.89–1.36)	396 : 419	1.11 (0.95–1.31)	1.08 (0.95–1.22)
Body mass index (BMI), kg/m^2					
<30	1741 : 1670	1[b]	1550 : 1865	1[b]	1[b]
≥30	247 : 200	1.26 (1.02–1.54)	331 : 347	1.28 (1.07–1.52)	1.26 (1.11–1.44)
Waist circumference, (cm)[c,d]					
<88			869 : 991	1[b]	1[b]
≥88			878 : 944	1.17 (1.02–1.35)	1.17 (1.02–1.35)
Waist circumference[d,e]					
<88 cm or BMI <30 kg/m^2			968 : 1215	1[b]	1[b]
≥88 cm or BMI ≥30 kg/m^2			913 : 997	1.28 (1.12–1.47)	1.22 (1.09–1.36)

[a]Estimates from logistic regression models adjusted for age, study center, study period, education, alcohol consumption, age at menarche, age at first birth, age at menopause, hormone replacement therapy use, and family history of breast cancer.
[b]Reference category.
[c]The sum does not add up to the total because of some missing values.
[d]Information on waist circumference not available in the first study.
[e]Defined as waist circumference ≥88 cm or body mass index ≥30 kg/m^2 for women with missing values for waist circumference.

Table 3 gives the distribution of cases and controls according to the number of MetS components and the corresponding ORs. In the two studies combined, compared with women without any MetS component, the OR of postmenopausal breast cancer was 1.07 (95% CI 0.96–1.18) for women with one MetS component, 1.24 (95% CI 1.08–1.43) for women with two components, and 1.75 (95% CI 1.37–2.22) for women with three or four components, with a significant trend in risk with increasing number of MetS components ($P < 0.0001$). The results were consistent across studies, the OR being 1.76 and 1.87, respectively, for women with three or more MetS components. When we defined MetS considering BMI instead of waist circumference in the second study too, the OR for women with three or more MetS components compared with women with no components became somewhat higher (OR = 1.96, 95% CI 1.34–2.85).

The association between MetS and postmenopausal breast cancer risk increased with age (Figure 1): the OR for women with three or more MetS components was 1.21 (95% CI 0.78–1.88) at age <60 years, 1.80 (95% CI 1.27–2.54) at age 60–69 years, and 3.04 (95% CI 1.75–5.29) at age ≥70 years.

Table 4 gives the OR for the number of MetS components in strata of education, alcohol consumption, age at menarche, at first birth and at menopause, HRT use, and family history. The risk was higher in women with no family history of breast cancer, while no difference in OR estimates emerged across strata of other covariates considered.

discussion

The present study—the largest available to date on MetS and breast cancer—provides evidence of an association between MetS and breast cancer risk in postmenopausal women. Moreover, it indicates that the association tends to increase with advancing age.

To our knowledge, only four other studies investigated the association between MetS as a single entity and the risk of postmenopausal breast cancer [7–10], suggesting as a whole an increased risk. Our results are also consistent with those from epidemiological studies which evaluated the association between individual components of MetS and breast cancer risk in postmenopausal women [5, 6].

Overweight/obesity—as measured by waist-to-hip ratio or BMI—is a recognized risk factor for breast cancer in postmenopausal women. The accumulation of visceral adipose tissue in postmenopausal women is related to the alteration of the concentration and availability of sex hormones after menopause [15].

Several studies evaluated the association between diabetes and risk of breast cancer, showing a direct relationship in postmenopausal women [5, 16, 17], though quantification remains difficult on account of possible residual confounding by overweight.

As in our study, a few other investigations showed an association between hypertension and the risk of breast cancer, particularly among postmenopausal women [18, 19], although the evidence is scantly.

Table 3. Distribution of 3869 postmenopausal women with breast cancer and 4082 postmenopausal controls, and corresponding odds ratios (ORs) with 95% confidence intervals (CIs), according to the number of metabolic syndrome (MetS) components (Italy and Switzerland, 1983–2007)

	First study (1983–1994)		Second study (1991–2007)		All
	Cases : controls	OR (95% CI)[a,b]	Cases : controls	OR (95% CI)[a,c]	OR (95% CI)[a,c]
No. of MetS components					
None	1160 : 1148	1[d]	624 : 782	1[d]	1[d]
1	594 : 564	1.04 (0.90–1.21)	711 : 867	1.13 (0.97–1.32)	1.07 (0.96–1.18)
2	196 : 135	1.46 (1.14–1.85)	393 : 444	1.25 (1.04–1.50)	1.24 (1.08–1.43)
≥3	38 : 23	1.76 (1.03–3.02)	153 : 119	1.87 (1.42–2.47)	1.75 (1.37–2.22)
P for trend		0.0021		<0.0001	<0.0001

[a]Estimates from logistic regression models adjusted for age, study center, study period, education, alcohol consumption, age at menarche, age at first birth, age at menopause, hormone replacement therapy use, and family history of breast cancer.
[b]MetS was defined as diabetes, hypertension, hyperlipidemia, and body mass index ≥30 kg/m^2.
[c]MetS was defined as diabetes, hypertension, hyperlipidemia, and waist circumference ≥88 cm or body mass index ≥30 kg/m^2 for women with missing information for waist circumference.
[d]Reference category.

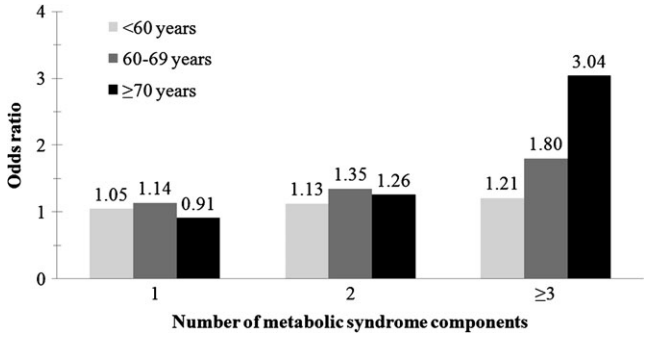

Figure 1. Odds ratios of postmenopausal breast cancer according to the number of metabolic syndrome components in different age groups. Odds ratios are estimates from logistic regression models adjusted for age, study center, study period, education, alcohol consumption, age at menarche, age at first birth, age at menopause, hormone replacement therapy use, and family history of breast cancer. Reference category: women without any component.

No association between hyperlipidemia and postmenopausal breast cancer risk was found in our data, while the results from other studies investigating serum cholesterol concentrations, hyperlipidemia, and postmenopausal breast cancer risk were controversial [20, 21].

The debate is still open whether MetS is a real syndrome or whether its components are isolated risk factors mediated through one common factor [22, 23], particularly overweight. It is still unclear whether MetS gives a greater risk than the sum of its components. However, the aggregation of the components appears to involve some additional risk in the present study.

Several mechanisms may explain the association between MetS and breast cancer risk in postmenopausal women. Obesity after menopause increases the risk of breast cancer by increasing the conversion of androgens to estrogens in peripheral adipose tissue and reducing sex-hormone-binding globulin (SHBG) with a consequent increase in the levels and availability of estrogens [15, 24, 25]. Other possible mechanisms involve hyperinsulinemia and insulin resistance. Serum glucose and insulin have been related to breast cancer risk in postmenopausal women. In the Women's Health Initiative, 6% random sample of women with measurement for glucose and insulin showed an approximate 2-fold RR for the highest tertile insulin [26]. The issue, however, is still unsettled since in a meta-analysis of five studies on insulin and breast cancer, two found a direct relation, but three no consistent association [5]. Insulin may promote cell proliferation in mammary epithelial cells and breast cancer cell lines through its mitogenic activity and by increasing the synthesis of insulin-like growth factor-I (IGF-I) [27]. Moreover, insulin reduces SHBG production and testosterone levels [28]. MetS is also associated with increased levels of leptin and decreased levels of adiponectin, which may promote breast cell proliferation [6]. The observation that the association between MetS and postmenopausal breast cancer risk tends to increase with advancing age is consistent with a duration–risk relationship in the exposure to high estrogen levels and other mechanisms of MetS-related carcinogenesis [24].

In our study, the definition of MetS was based on self-reported information from a questionnaire collecting history of diabetes, treated hypertension, and treated hyperlipidemia, rather than direct measurements of blood pressure, fasting plasma glucose, triglycerides, and HDL cholesterol. Although it was not possible to validate the information with medical records, drug treatment is considered a valid indicator of the presence of the above reported diseases [1]. Moreover, our results are consistent with studies that provided direct measurements of the components of MetS [7–10]. As a result of self-reported information, the prevalence of MetS is likely to be underestimated in our study since the definition adopted may have led to inclusion of subjects with more severe MetS only. Weight was also self-reported and may therefore be underestimated, particularly in overweight women [29]. Since information on waist circumference was available for ~90% of women of the second study only, we defined (abdominal) obesity as a BMI of ≥30 kg/m^2, instead of a waist circumference of ≥88 cm, for subjects with missing information on waist circumference [30]. There is, therefore, space for some misclassification of exposure in this study, though practically all women with BMI >30 kg/m^2 have a waist circumference ≥88 cm. Any nondifferential misclassification,

Table 4. Odds ratios (ORs) and their 95% confidence intervals (CIs) according to the metabolic syndrome (MetS) in strata of selected covariates (Italy and Switzerland, 1983–2007)

Covariates	No. of MetS components, OR (95% CI)[a]		
	1	2	≥3
Education (years)			
<7	1.07 (0.94–1.23)	1.22 (1.01–1.46)	1.81 (1.35–2.43)
≥7	1.05 (0.89–1.24)	1.28 (1.02–1.62)	1.64 (1.07–2.51)
Alcohol consumption (drinks/day)			
<1	1.01 (0.87–1.17)	1.20 (0.98–1.47)	1.88 (1.35–2.60)
≥1	1.14 (0.98–1.32)	1.30 (1.06–1.59)	1.53 (1.07–2.18)
Age at menarche (years)			
<12	1.23 (0.95–1.61)	1.49 (1.04–2.13)	2.17 (1.25–3.80)
≥12	1.04 (0.93–1.17)	1.21 (1.04–1.41)	1.66 (1.27–2.16)
Age at first birth (years)			
Nulliparous	1.04 (0.81–1.33)	1.42 (0.98–2.05)	0.82 (0.42–1.60)
<28	1.11 (0.96–1.27)	1.25 (1.03–1.50)	2.16 (1.59–2.93)
≥28	0.95 (0.77–1.18)	1.10 (0.83–1.46)	1.37 (0.83–2.25)
Age at menopause (years)			
<50	0.99 (0.84–1.15)	1.28 (1.04–1.59)	1.66 (1.16–2.35)
≥50	1.13 (0.98–1.30)	1.19 (0.98–1.44)	1.83 (1.31–2.55)
Hormone replacement therapy			
Never	1.05 (0.94–1.18)	1.22 (1.05–1.42)	1.78 (1.38–2.30)
Ever	1.26 (0.90–1.77)	1.49 (0.98–2.28)	1.71 (0.87–3.40)
Family history of breast cancer[b]			
No	1.08 (0.97–1.21)	1.27 (1.10–1.48)	1.86 (1.44–2.39)
Yes	0.97 (0.64–1.48)	1.00 (0.58–1.74)	0.92 (0.41–2.05)

[a]Estimates from logistic regression models adjusted for age, study center, education, alcohol consumption, age at menarche, age at first birth, age at menopause, hormone replacement therapy use, and family history of breast cancer. Reference category: no MetS component.
[b]*P* for interaction <0.05.

however, is likely to lead to an attenuation of any real association. With reference to recall bias, cases may report history of disease more frequently than controls, although this applies less to hospital-based controls, as they are similarly sensitized toward recalling diseases that occurred in the past [14]. Information on medical conditions provided by hospital controls has been proven to be satisfactorily reliable [31], and the interview setting does not substantially influence the recall of these information [32].

Among the strengths of our study are the large sample size, the similar catchment areas of cases and controls, the almost complete participation, and the availability of detailed information on various covariates. More important, the main results were consistent between the two studies, thus providing additional support for a real association. In conclusion, women with MetS have a higher breast cancer risk in postmenopause.

acknowledgement

The authors thank Mrs. I Garimoldi for editorial assistance.

funding

Italian Association for Cancer Research (10068 to C.L.V.) and the Swiss League and Research Against Cancer (OCS-01633-02-2005 to F.L.).

disclosure

The authors declare no conflicts of interest.

references

1. Alberti KG, Eckel RH, Grundy SM et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120: 1640–1645.
2. Pelucchi C, Negri E, Talamini R et al. Metabolic syndrome is associated with colorectal cancer in men. Eur J Cancer 2010; 46: 1866–1872.
3. Inoue M, Noda M, Kurahashi N et al. Impact of metabolic factors on subsequent cancer risk: results from a large-scale population-based cohort study in Japan. Eur J Cancer Prev 2009; 18: 240–247.
4. Rosato V, Zucchetto A, Bosetti C et al. Metabolic syndrome and endometrial cancer risk. Ann Oncol 2010. Published on October 11, 2010. PMID: 20937645.
5. Xue F, Michels KB. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. Am J Clin Nutr 2007; 86: s823–s835.
6. Vona-Davis L, Howard-McNatt M, Rose DP. Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. Obes Rev 2007; 8: 395–408.
7. Agnoli C, Berrino F, Abagnato CA et al. Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: a nested case-control study. Nutr Metab Cardiovasc Dis 2010; 20: 41–48.
8. Bjorge T, Lukanova A, Jonsson H et al. Metabolic syndrome and breast cancer in the Me-Can (metabolic syndrome and cancer) project. Cancer Epidemiol Biomarkers Prev 2010; 19: 1737–1745.

9. Kabat GC, Kim M, Chlebowski RT et al. A longitudinal study of the metabolic syndrome and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2009; 18: 2046–2053.
10. Capasso I, Esposito E, Pentimalli F et al. Metabolic syndrome affects breast-cancer risk in postmenopausal women: National Cancer Institute of Naples experience. Cancer Biol Ther 2011; 10: 1240–1243.
11. Franceschi S, la Vecchia C, Negri E et al. Breast cancer risk and history of selected medical conditions linked with female hormones. Eur J Cancer 1990; 26: 781–785.
12. Talamini R, Franceschi S, Favero A et al. Selected medical conditions and risk of breast cancer. Br J Cancer 1997; 75: 1699–1703.
13. Levi F, Pasche C, Lucchini F, La Vecchia C. Dietary intake of selected micronutrients and breast-cancer risk. Int J Cancer 2001; 91: 260–263.
14. Breslow NE, Day NE. Statistical Methods in Cancer Research. The Analysis of Case-Control Studies. Vol. 1 Lyon, France: IARC 1980; IARC Sci Publ No. 32.
15. Shen W, Punyanitya M, Silva AM et al. Sexual dimorphism of adipose tissue distribution across the lifespan: a cross-sectional whole-body magnetic resonance imaging study. Nutr Metab (Lond) 2009; 6: 17.
16. Wolf I, Sadetzki S, Catane R et al. Diabetes mellitus and breast cancer. Lancet Oncol 2005; 6: 103–111.
17. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer 2007; 121: 856–862.
18. Largent JA, McEligot AJ, Ziogas A et al. Hypertension, diuretics and breast cancer risk. J Hum Hypertens 2006; 20: 727–732.
19. Soler M, Chatenoud L, Negri E et al. Hypertension and hormone-related neoplasms in women. Hypertension 1999; 34: 320–325.
20. Eliassen AH, Colditz GA, Rosner B et al. Serum lipids, lipid-lowering drugs, and the risk of breast cancer. Arch Intern Med 2005; 165: 2264–2271.
21. Furberg AS, Veierod MB, Wilsgaard T et al. Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. J Natl Cancer Inst 2004; 96: 1152–1160.
22. Kahn R. Metabolic syndrome: is it a syndrome? Does it matter? Circulation 2007; 115: 1806–1810; discussion 1811.
23. Beaser RS, Levy P. Metabolic syndrome: a work in progress, but a useful construct. Circulation 2007; 115: 1812–1818; discussion 1818.
24. La Vecchia C, Negri E, Franceschi S et al. Body mass index and post-menopausal breast cancer: an age-specific analysis. Br J Cancer 1997; 75: 441–444.
25. Key TJ, Appleby PN, Reeves GK et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst 2003; 95: 1218–1226.
26. Kabat GC, Kim M, Caan BJ et al. Repeated measures of serum glucose and insulin in relation to postmenopausal breast cancer. Int J Cancer 2009; 125: 2704–2710.
27. Campagnoli C, Pasanini P, Peris C, Berrino F. Insuline-like growth factor I and breast cancer: epidemiological and clinical data. In Pasqualini JR (ed), Breast Cancer: Prognosis, Treatment and Prevention, 2nd edition. New York: Informa Healthcare 2008; 323–342.
28. Brand JS, van der Tweel I, Grobbee DE et al. Testosterone, sex hormone-binding globulin and the metabolic syndrome: a systematic review and meta-analysis of observational studies. Int J Epidemiol 2010. Published on September 24, 2010. PMID: 20870782.
29. Millar WJ. Distribution of body weight and height: comparison of estimates based on self-reported and observed measures. J Epidemiol Community Health 1986; 40: 319–323.
30. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome–a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006; 23: 469–480.
31. Bosetti C, Tavani A, Negri E et al. Reliability of data on medical conditions, menstrual and reproductive history provided by hospital controls. J Clin Epidemiol 2001; 54: 902–906.
32. Kelly JP, Rosenberg L, Kaufman DW, Shapiro S. Reliability of personal interview data in a hospital-based case-control study. Am J Epidemiol 1990; 131: 79–90.